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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,142	12/06/2006	Thomas Arendt	4121-180	5650

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
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EXAMINER	
MACFARLANE, STACEY NEE	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
10/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,142	ARENDT ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5 and 7-13* is/are pending in the application.

4a) Of the above claim(s) *9-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7 and 8* is/are rejected.

7)☒ Claim(s) *1, 2,8,13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 15, 2009 has been entered.

Response to Amendment

2. Claims 3 and 6 have been cancelled; Claims 1 and 2 have been amended as requested in the amendment filed on November 15, 2009. Following the amendment, claims 1, 2, 4, 5, and 7-13 are pending in the instant application.

Claims 9-13 were withdrawn from consideration as being drawn to a nonelected invention, in the Paper filed on May 29, 2008. Applicant is reminded that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 2, 4, 5, 7 and 8 are under examination in the instant office action.

Claim Objections

3. Claim 1 is objected to because the claim recites acronyms that are not spelled-out in their first use (i.e. PHA and PWM). It would be remedial to amend the claim

language to define the acronym in claim 1 so that the terms are more clearly understood.

4. Claims 2 and 13 are objected to because of the following informalities: Claim 2 appears to have been amended but the claim lacks a proper Status Identifier as set forth in 37 CFR 1.121(c). Claim 13 has been withdrawn from prosecution but also lacks the proper Status Identifier. The current status of all of the claims in the application, including any previously canceled or withdrawn claims, must be given. Status is indicated in a parenthetical expression following the claim number by one of the following status identifiers: (original), (currently amended), (previously presented), (canceled), (withdrawn), (new), or (not entered). Appropriate correction is required.

5. Claims 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim (35 U.S.C. 112, fourth paragraph). Claim 1 part (b) recites simple cell quantification, and part (d) recites use of a CD69 antibody for quantification for a single protein. However, claim 8 depends from claim 1 and adds quantifications of total protein content or total nucleic acid content. Therefore, claims 8 can be infringed by a method comprising quantifying nucleic acid, which does not infringe claim 1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. See MPEP § 608.01(n). The test for a proper dependent claim is whether the dependent claim includes every limitation of the parent claim. A proper dependent claim shall not conceivably be infringed by anything, which would not also infringe the basic claim.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 4, 5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is vague and indefinite for the following reasons. Step (b) recites "quantification of lymphocytes within the cell population comprising the CD69 for mitogenic stimulation"; step (d) recites "quantification of lymphocytes within the mitogenically stimulated cell population comprising the CD69 after step (c)". There's no antecedent basis for "the cell population" or "the CD69" in step (b), "the cell population" in step (c). Additionally, there is a discrepancy of terminology between the "patient sample" in part (a) and the "cell population" in the other steps. It is suggested that Applicant amend part (a) to recite "obtaining a sample from a patient, wherein the sample comprises a cell population comprising lymphocytes."

9. Claim 1 is further vague and indefinite in that it recites calculating a "quotient of the number of lymphocytes bearing CD69 in step (b) and step (d)". It is unclear whether the quotient is calculated by dividing the number obtained from step (b) by the number obtained from step (d), or vice versa.

10. Claim 1 is further indefinite in that it is missing a method step whereby the detected stimulation index is related to a diagnosis of Alzheimer's or predisposition for said disease, as recited in the preamble. Thus, the method step that results in a diagnosis is missing from the claim.

11. Claim 4 is indefinite for depending from a canceled claim.

12. Claims 4 and 5 do not further limit the method of the parent claim. Rather, these claims recite additional steps and raise the question of whether these additional steps are required in order for the method to be successful, or whether they may be omitted since they are absent from the base claim. Furthermore, it is not clear if claim 4 requires an additional method step to screen for or otherwise select lymphocytes expressing CD4 and/or CD8 or, alternatively, if claim 4 merely further characterizes the lymphocytes already isolated and quantified in the method of claim 1. Amending claim 4 to recite the method of claim 1 further comprising quantifying the lymphocytes from part (b) for the surface markers CD4 and/or CD8 would resolve this issue for claim 4. Amending claim 5 to recite a method of claim 2 further comprising stabilizing the blood by adding one or more anticoagulative compounds to the sample after step (a) and before step (b) would resolve the issue for claim 5.

13. Claims 2, 7 and 8 are indefinite for depending from indefinite claims.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As currently amended to recite the specific cell surface marker CD69 and specific mitogenic agents, the rejection of Claims 1, 2 and 4-8 under 35 U.S.C. 112, first paragraph, written description requirement, is withdrawn.

13. As currently amended, Claims 1, 2, 4, 5, 7 and 8 stand as rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of quantifying cells expressing the surface marker CD69, comprising obtaining a cell sample, quantifying cells within the sample expressing CD69, and optionally further comprising the steps of stimulating the cells by PHA or PWM, quantifying cells expressing the surface marker CD69, and calculating the difference in the number of cells expressing CD69, does not reasonably provide enablement for diagnosing Alzheimer's disease or an early stage or predisposition with a reasonable expectation of success.

On pages 6-7 of Remarks filed November 15, 2009, Applicant traverses the rejection on the grounds that the claims as currently amended meet the enablement requirement, and that the subject matter of the claims is sufficiently supported by the specification. Additionally, Applicant provides a declaration describing a post-filing study performed and asserted to provide enabling support for the method.

While these arguments and evidence have been fully considered they are not persuasive to overcome the rejection for the following reasons. The scope of the instant claims is broadly drawn to diagnosing not only disease in those who have clinical manifestations of Alzheimer's disease, but also in those subjects who are at an early

stage or even those who merely have a predisposition for developing the disease later in life. Within the base claim, there are no requisite criteria or method step for determining patients and the broadest reasonable interpretation of the method is that it can be performed in the general population with a reasonable expectation of success of diagnosing a predisposition for developing Alzheimer's disease. Since the etiology of Alzheimer's disease pathology has yet to be elucidated, and there is no record of a nexus between lymphocyte CD69 expression and Alzheimer's pathology, then one of ordinary skill in the art would have to make a substantial inventive contribution in order to demonstrate that the method as claimed can diagnose a predisposition for developing Alzheimer's pathology with a reasonable expectation of success.

The Declaration of Dr. Arendt under 37 CFR 1.132 filed November 15, 2009 is insufficient to overcome the rejection of claims 1, 2, 4, 5, 7 and 8 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action because: The post-filing data uses methodology that is not disclosed within the four corners of application as filed. In the first full paragraph on page 7 of Remarks, Applicant states that for the experiments disclosed within the Declaration "the samples were prepared according to the example of the specification (pages 7-9)". However, Applicant goes on to state that the method required that the Alzheimer's disease patient group be identified using ICD-10 research criteria. This specific methodology is neither disclosed within the instant application nor required by the method steps. While the post-filing data may provide evidence that CD69 stimulation index of more than 10 correlates with a clinical classification of Alzheimer's disease (ICD-10), it provides no enabling support for the

method of diagnosis in patients without clinical manifestations, such as those with early stage disease or merely a predisposition for said disease later in life. Thus, there is no evidence in support for the method being enabled commensurate in scope with the breadth of the claims.

Additionally, as noted in section 10 above, Claims 4 and 5 recite additional method steps that are not included within the base claim. Since a method that does not comprise these steps is claimed separately, it is unclear whether these steps are essential for providing a diagnosis of Alzheimer's disease/early stage/predisposition for disease. There is no nexus provided within the instant disclosure as to how the numbers of CD4+ and/or CD8+ subpopulations relates to Alzheimer's disease (AD) etiology (claim 4); nor is there any evidence of record regarding the addition of anti-coagulative compounds and determining AD pathology and diagnosis.

Within the art at the time of filing, it was well-known that monocytes/macrophages in patients with Alzheimer's disease (AD) display elevated percentages of CD69 positivity (Kusdra et al., Immunobiology, 202:26-33, 2000). The Kusdra et al. reference, however, teaches that many diseases have a prominent inflammatory component and that similar level of elevated CD69 reactivity is observed in AIDS dementia patients (page 31). The Kusdra et al. reference goes on to conclude that "CD69+ cells may not contribute directly to AD pathogenesis and may be the result of proinflammatory processes in the brain. Since these patients already have an AD diagnosis, it is difficult to determine whether CD69+ would make a good marker for risk assessment before AD onset". The same is true for the method of the instant claims.

The post-filing data merely demonstrate that patients with confirmed AD had a stimulation index of more than 10, but they provide no evidence that the method can successfully predict a predisposition for AD prior to clinical onset, or that the stimulation index is positively correlated with scores for early stage dementia (i.e. Mini-Mental State Examination scores between 21 and 24). Prior to filing, methods comprising stimulation of peripheral lymphocytes with the instantly-elected PWM, quantification of the cells by cell sorting using the surface marker CD69 and further specifying and separating cells as CD4+ and/or CD8+ subpopulations via flow cytometry using monoclonal antibodies were well known in the art (Neubert et al., 2000, cited in previous Office action mailed 7/31/2008). It was also well-recognized that the method could be practiced using samples from patients with Alzheimer's disease with respect to "potentially diagnostic purposes" (Stieler et al. 2001, and cited as reference AF on the IDS filed 9/5/2006). There was nothing of record to suggest that a definitive diagnosis of Alzheimer's disease or of early stage dementia or merely a predisposition for disease could be provided by the method as claimed.

Examiner maintains that the guidance within the disclosure as filed is merely speculative and postulates how the invention may work but does not provide guidance to one of ordinary skill in the art that the method can be performed with a reasonable expectation of success of diagnosing Alzheimer's disease, early onset dementia, or a predisposition for developing Alzheimer's disease later in life. Therefore, the rejection is maintained.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-R 5:45 to 3:30, TELEWORK-Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/Elizabeth C. Kemmerer/
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